ATTACHMENT A

The Oncologist, Vol. 7, Suppl 3, 20-33, August 2002

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Cancer Vaccines

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Learning Objectives

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After completing this course, the reader will be able to:

1. Explain the relationship between the tumor and host immune system.
2. Recognize the mechanisms by which tumor cells escape the immune surveillance.
3. Recognize the potential of vaccines in the treatment and prevention of cancer.

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Although cancer immunotherapy was initiated by *William Coley* more than a century ago, the field of cancer vaccines is in an early stage of development. Only recently, major advances in cellular and molecular immunology have allowed a comprehensive understanding of the complex and high rate of interactions between the immune system and tumor cells. We have learned that these tumor–immune system interactions may result either in strong immune antitumor response or tolerance to tumor-associated antigens. This article will discuss the profound interest in cancer vaccines derived from their potential to induce antitumor responses in vivo. Substantial data from several preclinical

models and early human clinical trials have confirmed the ability of cancer vaccines to induce immune responses that are tumor-specific and, in some cases, associated with clinical responses. One future challenge will be to determine how to appropriately stimulate the pathways leading to effective interaction among antigen-presenting cells, T lymphocytes, and tumor cells. It also is critical to develop monitoring strategies that may allow the identification of patients who may benefit from cancer vaccines.

Key Words: Cancer· Vaccines· Immunotherapy· Dendritic cells

Introduction

The observation that some human tumors experience spontaneous regression suggests that the immune system may have the potential to protect against the uncontrolled growth of cells that have undergone neoplastic transformation [1, 2]. Central to this long-held basic paradigm of immunology is the ability of the immune system to recognize tumor-associated antigens (TAA) displayed on human malignancies and to direct cytotoxic responses to these targets. These recognizable antigens may range from short, three-dimensional structures that are identified by antibodies to even smaller amino acid sequences that are discernible by cytotoxic T lymphocytes (CTLs) [3–6].

Although antibodies alone or in combination with chemotherapy can be highly effective in mediating tumor regression in hematologic malignancies [7–10], their effects on solid tumors have been less effective. Moreover, most responsive solid tumors are malignancies that overexpress certain growth factor receptors [11]. T-cell-mediated immune responses seem to have a greater potential for eradicating tumor cells. Therefore, a significant amount of preclinical and clinical research is focused on inducing a cellular antitumor immune response, and one of the main goals of cancer immunotherapy is to generate highly specific CTLs.

Several clinical trials of immunotherapy in cancer patients have attempted to activate the immune system in an effort to elicit an effective antitumor response. The majority of these clinical trials focused on the effector phase of the immune response, specifically the activation and/or generation of cells with cytotoxic capabilities such as natural killer (NK) cells, lymphokine-activated killer cells, and tumor-infiltrating lymphocytes. It is clear from trials using interleukin-2 (IL-2) that immune manipulation can induce durable major responses or even cure a subset of patients with extensive metastatic renal carcinoma or melanoma [12–15].

Generation of CTLs is a complex process that requires a minimum of two signals. The first signal, recognition, is mediated by interaction of the T-cell receptor with a specific antigenic peptide presented on the antigenpresenting cell (APC) in the context of the HLA, the human major histocompatibility complex (MHC) [16]. The second signal, costimulation, is delivered by APCs through members of the B7 family and various adhesion molecules [17–20] (Fig. 1A). If costimulation is not administered, T

cells may enter a state of anergy [20–23], which may result in tolerance to tumor antigens and failure to halt tumor growth (Fig. 1B). It is noteworthy that in tumor-bearing hosts, TAA are presented either by APCs or tumors themselves in a fashion in which costimulation and/or other critical signals to T cells are not effectively delivered [24–26]. Thus, the default response of the immune system after interacting with tumor cells is anergy and consequently the development of tolerance. The present challenge for the immunotherapy of cancer is to overcome the barriers that prevent the appropriate recognition and elimination of neoplastic cells.

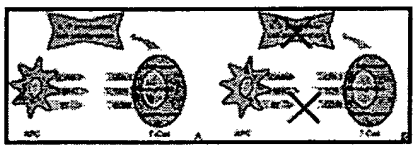

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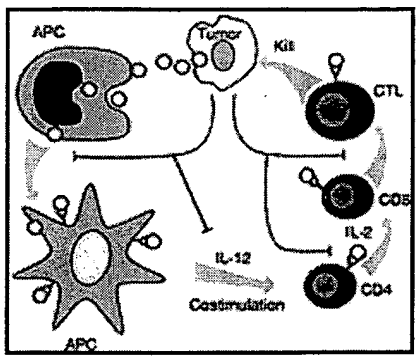
Figure 1. T-cell activation by antigen-presenting cells requires a close APC–T-cell interaction and the delivery of recognition and costimulatory signals (A). *T-cell anergy occurs when the recognition signal is given in the absence of costimulation (B).*

Cancer Vaccines

Tumor–Host Interaction

Tumor cells are genetically unstable and do not have efficient mechanisms that protect against this instability [27–29]. As a result, a small percentage of tumor cells will undergo apoptosis and release apoptotic bodies containing TAA that are taken up by immature APCs. In the presence of the appropriate cytokine microenvironment, immature APCs may become mature APCs and deliver costimulation signals resulting in the generation of T cells with an activated phenotype. Activated CD4 cells produce an array of cytokines leading to the generation and clonal expansion of TAA-specific CTLs that will recognize and kill tumor cells (Fig. 2). Unfortunately, cancer cells, under the selective pressure of the immune system, have developed mechanisms allowing them to avoid being targeted by the immune system (Table 1). Furthermore, tumor cells, in sharp contrast with bacteria or viruses, do not induce the proinflammatory cytokines and chemokines required for the proper interaction between APCs and antigen-specific reactive T cells [30–32].

Figure 2. Potential interactions between the tumor and the immune system. *Apoptotic bodies derived from tumor cells are taken up and processed by immature APCs. Upon maturation, APCs deliver recognition and costimulatory signals to CD4 T cells in the presence of cytokines that favor the development of CTLs. By producing factors that interfere with the maturation process of APCs and the delivery of recognition and costimulatory signals, tumor cells may affect*



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the generation of CTLs and escape the immune response.

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Table 1. Potential barriers to cancer vaccine: tumors escape the immune system

Pioneering studies performed by *Dr. William Coley* more than 100 years ago clearly established the curative potential of bacteria and bacteria lysates in patients with cancer [33, 34]. It is now known that *Coley's* toxin was not directly responsible for the antitumor effects observed. Rather, some of the bacterial products, which were very potent at activating the immune system, destroyed the tumors [35]. Decades later, *Tokunaga et al.* demonstrated that bacterial DNA alone could account for the immunomodulatory and antitumor properties of BCG [36]. More recently, studies with antisense oligodeoxynucleotides (ODN) revealed that CpG dinucleotides were potent stimulators of B cells [37], NK cells [37], and APCs [38, 39]. Furthermore, CpG DNA induces innate immune resistance to tumors as well as the regression of established tumors in mice [40, 41]. Many investigators are now using cancer vaccines to overcome some of the barriers to successful cancer immunotherapy by mimicking the proinflammatory responses generated by the innate immune system when exposed to tissue-destructive viral and bacterial infections. The ultimate goal of vaccine strategies is to convert a tolerant T cell to a fully aware and activated TAA-specific T cell that would be the most effective antitumor effector cell.

Based on preclinical and clinical research, a large number of cancer vaccine clinical trials involving different tumor types and various vaccine strategies currently are being conducted. The increasing number of TAA (Table 2) and strategies (Table 3) prevents detailed discussion of all the clinical information available. Melanoma is one of the best-studied malignancies in the cancer immunology field, and almost all existent immunotherapy strategies have been tested in patients with this disease because it is one of the human malignancies to which immune responses can be demonstrated consistently. Therefore, using melanoma as a model, we will discuss some of the vaccine approaches available for the treatment of cancer. We also will discuss other diseases with unique characteristics not commonly found in melanoma.

View this table: **Table 2.** Potential targets for cancer vaccines
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View this table: **Table 3.** Cancer vaccines: strategies
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The development of therapies specifically targeting TAA has the advantage that the immune response would be directed mainly against the tumor cells and few other normal tissues. However, one potential major disadvantage of peptide vaccines is the possibility of raising an irrelevant peptide-specific response. For instance, it was reported that patients immunized with her2 peptide developed her2-specific T-cell responses; however, the reactive T cells failed to recognize her2+ tumor cells [42, 43]. This suggests that the peptide may not be processed naturally by the tumor cell. This disadvantage is of particular concern when using tailored peptides from patient-specific mutated proteins, i.e., p53 and ras. Several melanoma antigens have been identified and generally could be classified into cancer testes antigens [44–46], differentiation antigens [47–51], and mutated antigens or atypical transcripts antigens [52–54] (Table 2⊞). The cloning of the genes encoding cancer antigens has provided new possibilities for cancer treatment.

Vaccine trials using some of the aforementioned antigens recently have begun and are providing substantial information about the type of immune responses that are elicited. These studies are in relatively early stages and only a few vaccines have entered later stages of clinical testing. Although current results are not final, some conclusions can be drawn. First, CTL responses can be induced by peptide vaccination [43, 55, 56]; second, the presence of an expanded pool of TAA-specific T cells does not lead to tumor regression [57–59]; third, increasing the affinity of the peptide for the MHC can greatly increase the potency of a vaccine by converting a subdominant epitope into a dominant one [4, 60, 61]. Using a modified gp100 peptide, *Rosenberg et al.* elicited peptide-induced T-cell responses in 91% of patients immunized. In contrast, vaccination with the unmodified peptide failed to induce a T-cell response in most patients [4]. Lastly, peptide-based vaccinations by themselves have not demonstrated clinical efficacy unless combined with IL-2 administration. In fact, a clinical trial conducted at the National Cancer Institute (NCI) reported that administration of high-dose IL-2 following s.c. administration of the modified peptide resulted in a clinical response of 42%, whereas no clinical responses were observed in patients receiving the modified peptide alone. Curiously, however, patients who achieved clinical response had a decreased T-cell response. The authors believed that the

decreased response was due to homing of the reactive T cells to the tumor site [4]. Randomized clinical studies are currently under way at the NCI to ascertain the contribution of each component of the treatment to the observed response.

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Immunizations with nonpeptide antigens also have been used against melanoma. Gangliosides are sialated glycolipid antigens expressed on normal cells of neural crest origin and highly expressed on melanoma. Among the gangliosides, GM2 has been found to be the most immunogenic and has been the target of several vaccination clinical trials in the adjuvant setting for patients with melanoma at high risk for recurrence. For example, a double-blind randomized clinical trial in patients with resected stage III melanoma compared patients treated with GM2/BCG with patients receiving BCG alone. The study demonstrated that immunization with GM2/BCG induced GM2 antibody in 64% of patients, while only 11% of patients treated with BCG alone developed antibodies. The antibody production was associated with prolonged disease-free interval (DFI) and survival. However, there were no statistically significant differences between treatments in either DFI or survival [62]. This study led to the design of a large prospective, randomized, intergroup trial evaluating high-dose interferon-α2b (IFN-α2b) (HDI) versus vaccination with GM2 conjugated to keyhole limpet hemocyanin (KLH) and administered with QS-21 as adjuvant [63]. The trial had a median follow-up of 16 months and was closed after an interim analysis revealed the superiority of HDI compared with GM2 vaccination.

The idea of combining IFN-α2b and GM2 vaccinations is very appealing. However, there has been a concern that IFN-α could reduce the humoral response induced by the vaccine. A recent report by *Kirkwood et al.* specifically addressed this concern and reported that IFN-α combined with GM2 immunization does not decrease antibody response to GM2 vaccination [64]. The combination also seems to improve DFI; however, inasmuch as IFN-α2b alone was not tested, it is not known whether the benefit was due to IFN-α2b, or an additive or synergistic effect with the vaccine exists. Future randomized studies will address this question.

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Patients with cancer have multiple alterations of the immune system that may compromise the recognition and elimination of tumor cells [65, 66]. Additionally, tumor cells by themselves may induce tolerance [67, 68]. These characteristics of both the immune system and the tumor cell likely contribute to tumor growth. One of the relatively new approaches to enhancing the antitumor response is to provide cells that may facilitate the creation of the proper microenvironment with the potential to overcome tumor-induced

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tolerance. Cancer cellular vaccines can be packaged in at least three forms: 1) dendritic cells (DCs); 2) autologous or allogeneic tumor cells, and 3) tumor-APC hybrids. The cellular vaccines are manipulated ex vivo and then administered to patients via different routes. Cellular vaccines are in the early stages of development for cancer treatment and here we will summarize some of the approaches that have been taken to the clinic. We will not discuss approaches involving the use of recombinant DNA alone (naked DNA) or tumor RNA.

Dendritic Cells

Attempts to increase the efficacy of peptide vaccines have lead to the use of APCs as delivery vehicles and cellular adjuvants (Fig. 3⊞). DCs are professional APCs that play a crucial role in the initiation of the immune response through the uptake, processing, and presentation of tumor antigens to T cells. DCs have been described as the most potent and efficient APCs capable of activating both resting and naïve T cells [69, 70]. Preclinical studies have clearly demonstrated that antigen-pulsed DCs can generate protective immunity against tumors [71–73]. More recently, pilot studies performed in various types of cancer including melanoma [74–76], lymphoma [77, 78], multiple myeloma [79, 80], colon cancer [81], prostate cancer [82–86], and glioblastoma [87] suggest that monocyte-derived DCs are capable of eliciting antigen-specific immune responses in humans, some of which are associated with clinical responses. The majority of the clinical trials using the DC-based cancer vaccine approach have been performed in patients with metastatic melanoma. Although early studies using peptide-pulsed DC clearly demonstrated antigen-specific immune responses both to the immunizing peptide and to autologous tumor, no clinical responses were observed [75]. More recently, a better understanding of the biology of DCs and a major improvement in the culture and administration conditions of these cells have occurred, paving the way for more rationally designed clinical trials.

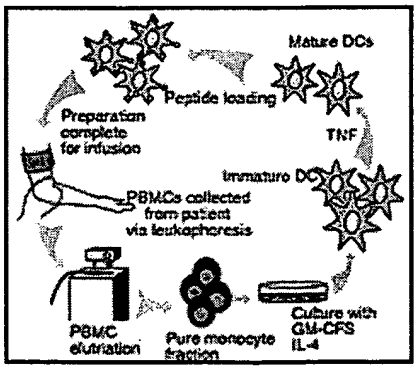

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Figure 3. Adoptive immunotherapy with autologous monocyte-derived DCs. *Peripheral blood mononuclear cells (PBMCs) are collected by leukopheresis. Monocytes are purified by elutriation and induced to differentiate into mature DCs with cytokines. Dendritic cells are then pulsed with peptides or tumor lysates and infused back to patients.*

It is known now that the maturation stage of DCs is quite relevant. Whereas immature cells are better suited to take up and process antigens, mature DCs are better at presenting antigens [69]. Recently, *Nestle et al.* reported on a clinical trial involving 16 patients with metastatic melanoma who received a

DC-based cancer vaccine [76]. Twelve patients received DCs loaded with multiple melanoma-associated peptides (either HLA-A2-binding peptides such as tyrosinase, MART-1, and gp100 or HLA-A1-binding peptides such as MAGE-1 and MAGE-3), and four patients received tumor lysates instead of peptides. The rationale behind the use of multiple peptides or tumor lysates was to decrease the chances of the tumor escaping the immune response by acquiring single-point mutations. Because primary immune responses occur in lymphoid organs, *Nestle et al.* delivered the DC preparation (1×10^6 cells) into an inguinal lymph node or in close proximity to the regional lymph node. Patients were immunized once weekly for 4 weeks, followed by booster immunizations given after 2 weeks and thereafter in monthly intervals for up to 10 vaccinations. Treatment was well tolerated, with only occasional mild fever or swelling at the injection site that lasted 1 to 2 days. The use of self-antigens or tumor lysates has the potential of breaking tolerance and inducing autoimmunity. Although clinical evidence of autoimmunity was not observed, anti-thyroid stimulating hormone (TSH) receptor antibodies and antinuclear antibodies were detected in a few patients thus raising the need for caution. Eleven of 16 patients immunized with the DC preparation developed a positive delayed-type hypersensitivity (DTH) response. More importantly, regression of lesions in pancreas, lung, and skin were observed in six patients (two complete responses [CRs], three partial responses [PRs], and one minor response) with some responses lasting more than 15 months. The observed clinical responses were accompanied by antigen-specific reactivity. Two of five responders received DCs pulsed with tumor lysates in which the identity of the relevant TAA is not known. These results suggest that similar approaches could be used in the setting of tumors lacking well-characterized antigens.

Although the study of *Nestle et al.* is clearly relevant, the small number of patients limits the conclusions that can be drawn. Nevertheless, this pilot study demonstrates that DC-based cancer vaccines must be further explored to define the best strategies to be used with this approach. Several variables should be evaluated, including: 1) the type of DC to be used; 2) the type of adjuvant; 3) the cytokine(s) to be administered, and 4) the method of providing TAA, i.e., peptides, tumor lysates, RNA, DNA, etc. Significant clinical effort and time will be required to answer these fundamental questions.

Tumor Cells

Autologous and allogeneic tumor cells were one of the first types of tumor vaccines to be used [88–90]. Theoretically, the main advantage of tumor cell vaccines is that they have all the relevant tumor antigens needed by the immune system to mount an effective antitumor response. This is particularly true if autologous tumor cells are used instead of allogeneic tumor cells. A second advantage is that tumor cell-based immunization allows the development of cancer vaccines without knowing the specific antigens. The advantages of tumor cell-based cancer vaccines must be balanced against two major disadvantages: the potential for autoimmunity and the potential for increasing the anergic status of the T cells due to the lack of functional costimulatory molecules on tumor cells.

Initial attempts to immunize cancer patients with tumor cells were disappointing [88–90] and temporarily decreased interest in the field. The lack of effectiveness could be explained by the inability of tumor cells to create an inflammatory response that attracts APCs to the tumor site where they could take up, process, and present TAA to T cells within the context of the MHC and in the presence of the

constitutively expressed costimulatory molecules. To test whether the addition of nonspecific bacterial adjuvants could improve the outcome of this approach, a prospective randomized trial was conducted in patients with Duke's stage B and C colon cancer [91]. Four weeks after surgery, 254 patients were randomly assigned to receive autologous vaccine plus BCG or no adjuvant treatment. Three weekly vaccinations were given followed by a booster vaccination at 6 months. Patients with Duke's stage B disease who received the vaccine had a significant improvement in recurrence-free survival ($p = .0032$) compared with patients who did not receive the vaccine. There was no benefit for patients with Duke's stage C disease.

More recently, a phase III clinical trial with a similar cohort of patients was conducted by the Eastern Cooperative Oncology Group [92]. In this study, 412 patients (297 with stage II disease and 115 with stage III disease) were randomized to receive intradermal vaccine injections or no vaccine three times weekly 4 weeks after surgery. After a 7.6-year median follow-up period, there were no significant differences in clinical outcomes between the two arms. However, subset analysis, with all its caveats and pitfalls, revealed that patients mounting a potent DTH to the vaccine have a 5-year survival advantage compared with patients who did not have a DTH. Taken together, these studies suggest that a subset of patients may benefit from autologous colon cancer vaccines. They also suggest that the addition of nonspecific adjuvants to autologous cancer vaccines has not resulted in a major breakthrough; therefore, other avenues have been explored.

In vitro and preclinical studies have provided evidence that genetically modified tumor cells display an increased immunogenicity [93–98]. The modifications are aimed to counteract some of the defects found in tumor cells that prevent them either from acting as professional APCs or being targeted by CTLs: low or undetectable MHC expression, lack of costimulatory molecules, and inability to produce cytokines required for DC maturation GM-CSF, IL-4, tumor necrosis factor [TNF]) or T helper (Th)1 polarization (IL-12). The knowledge generated from preclinical models has resulted in the development of several clinical trials [99–102]. The goals of these clinical trials are to evaluate the safety and define the toxicities associated with the administration of genetically modified tumor cells. Initial reports demonstrated that the approach is safe and associated with only minor local toxicities.

Simons et al. performed a randomized, double-blind, phase I clinical trial that evaluated the safety of and immune response to an autologous renal cell carcinoma (RCC) vaccine modified with the GM-CSF gene [100]. Eighteen patients received equivalent doses of irradiated autologous RCC cells with or without ex vivo human GM-CSF gene transfer. No dose-limiting toxicities were observed. Histopathology of the vaccine site at day 7 revealed that $CD3^+$ cells and DC infiltration were increased in the GM-CSF-transduced vaccine relative to the nontransduced cells. Furthermore, an intense eosinophil infiltrate was observed at the vaccine site of the transduced vaccine compared with the nontransduced vaccine. Interestingly, preclinical models have suggested that the eosinophil infiltrate is relevant and associated with antitumor immunity [103]. One patient had a PR with regression of multiple pulmonary metastases. Of note, this particular subject experienced intense pruritus at the vaccine site after receiving the third cycle of GM-CSF-transduced vaccine.

A major limitation of this trial and many others using autologous tumor cells is the low yield of autologous tumor cells that may compromise the number of immunizations given to the patients. A second inconvenience is the variability of GM-CSF secretion among patients, which could be responsible for the different levels of responses observed. Although autologous tumor cells are arguably the best source of TAA for cancer vaccine development, limitations plus the major time and expense required for the approval of each patient's vaccine by the appropriate regulatory agencies severely limits the development of this type of immunization approach.

To overcome some of these problems, basic and clinical investigators have explored other alternatives: namely, allogeneic tumor cell vaccines, tumor-APC fusion strategies, and mixed autologous-allogeneic tumor vaccines. The allogeneic approach is very attractive because it would allow the produced vaccine to be stored and ready for use when needed for the patient's immunization. Moreover, because many TAA seem to be shared among different patients' tumors [104–106], allogeneic vaccines, similar to autologous vaccines and in contrast with peptide vaccines, may allow bypassing the need to identify tumor antigens that actually are not known for the most common cancers. Finally, the efficacy of allogeneic vaccines has been established in preclinical models [93, 107, 108]. Several human studies using this approach recently have been initiated and/or reported [99–102, 109].

Jaffee et al. conducted a phase I trial of safety and immune activation in 14 patients with stage II or stage III pancreatic adenocarcinoma who underwent tumor resection followed by vaccination with two allogeneic pancreatic cancer cell lines [101]. The first vaccination occurred 8 weeks after the resection of the primary tumor followed by adjuvant chemoradiation. The second, third, and fourth vaccinations were given at weeks 40, 44, and 48, respectively. Six of 14 patients had no evidence of disease after completing the first vaccination and adjuvant chemoradiation and, therefore, were eligible to continue within the protocol. No systemic toxicities were observed. Four of five patients who received the highest dose of cells (50×10^7) were the only subjects to develop detectable serum levels of GM-CSF. Although efficacy was not the primary objective of this trial, four patients were disease-free for more than 25 months after diagnosis. Interestingly, these patients received some of the highest doses of allogeneic cells, and they also developed the largest DTH reactions against autologous tumor cells. The study demonstrated that the approach is safe and, at high doses, the allogeneic vaccine produced a remarkable DTH response against autologous tumor suggestive of antitumor immunity.

Tumor-APC Hybrids

A novel development in cancer vaccines is the use of tumor-APC fusion technology. The vaccine is produced by exposing tumor cells and APCs to polyethylene glycol (PEG) or electrical fields, which results in the generation of a tumor-APC hybrid. The rationale behind this approach is that the resulting hybrid will have the appropriate TAA derived from the tumor and the unparalleled costimulatory capabilities of the APCs.

Preclinical studies have provided the rationale for the use of cell hybrids in the

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cancer vaccine setting [110–112]. More importantly, the tumor-APC strategy already has been associated with major clinical responses in patients with metastatic renal carcinoma [113]. In a pilot study, 17 patients received the vaccine SC in close proximity to inguinal lymph nodes. Six weeks later, patients received a booster immunization and underwent reevaluation. Patients without evidence of progressive disease continued with booster immunization every 3 months. The vaccine was well tolerated, with no significant toxicities or evidence of autoimmune disease. No patient had a DTH response after autologous tumor challenge before vaccination; however, 11 of 17 patients presented a positive DTH response after vaccination. Seven of the 11 patients who developed a DTH response had a complete or partial tumor response. In summary, 41% of the patients responded to the tumor-APC hybrid strategy with four CRs, two PRs, and one mixed response. With a median follow-up of 13 months, three of the four patients with CRs have remained without evidence of disease for up to 21 months. These impressive results in patients with advanced disease indicate that tumor-APC hybrid vaccination is a safe and effective therapy for metastatic renal carcinoma and warrants the development of prospective trials to further assess long-term efficacy.

Although the tumor-APC hybrid strategy has enormous potential, there are several questions that need to be addressed if this approach is to become widely used in clinical trials. For instance, which type of fusion technology must be used to generate the hybrids—PEG or electrofusion? What are the best APCs for the hybrid—mature cells that are better at presenting antigens or immature cells that may be better at trafficking to lymph nodes [114]? Which will be the best tumor source for the hybrid—autologous tumor cells with their potential for producing factors that negatively affect APC function and maturation or well-defined allogeneic-generic tumor cells for off-the-shelf use? Despite all these important and unanswered questions concerning this novel approach, the impressive results observed in early pilot studies encourage more clinical and basic research.

Idiotype Vaccination

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Immunoglobulin (Ig) molecules contain highly specific, unique peptide sequences in their variable regions at the antigen-combining sites in the complementary-determining regions. The variable regions of heavy and light chains combine to form the unique antigen recognition site of the Ig protein. These variable regions contain determinants that themselves can be recognized as antigens, or idiotypes. Non-Hodgkin's lymphomas are usually clonal proliferations of B cells synthesizing a single type of antibody molecule with a unique variable region that can serve as tumor-specific antigen [115] and, therefore, can be targeted for cancer vaccination. Follicular lymphomas also are associated with a characteristic translocation that brings the *bcl-2* gene on chromosome 18 under the transcriptional control of the Ig heavy-chain gene located in chromosome 14. This translocation, t(14-18), has been used as a molecular marker for minimal residual disease [116]. Most patients with follicular lymphoma in CR after conventional chemotherapy still have cells displaying the t(14-18) detectable by polymerase chain reaction (PCR) [117] and seem to be at increased risk of relapse.

The first clinical trial of idiotype vaccination included patients with low-grade follicular lymphoma in first remission [118]. Monitoring humoral and cellular responses to the vaccine revealed that 14 of 32 patients mounted predominately anti-idiotype humoral responses rather than T-cell proliferative responses to their autologous tumor idiotype protein. A recent analysis of these 32 patients demonstrated an improved clinical outcome for those patients who mounted a specific immune response [119]. A second pilot clinical trial using this approach in patients in CR after chemotherapy with the PACE regimen (prednisone, doxorubicin, cyclophosphamide, etoposide) has been reported [120]. Twenty chemotherapy-naïve patients with stage III/IV follicular lymphoma underwent lymph node collections and were treated with PACE to CR plus two additional cycles. After immune recovery, each patient received four monthly vaccinations with the lymphoma-associated Ig idiotype with KLH plus GM-CSF as adjuvant. Eleven of the 20 patients were found to have a detectable translocation in their primary tumors. All 11 patients had evidence of the malignant clone by PCR both at diagnosis and after chemotherapy, yet they were in complete clinical remission. After the vaccinations, 8 of the 11 patients achieved and sustained molecular remission. Moreover, $CD4^+$ tumor-specific cells also were induced by vaccination.

Although the long-term clinical relevance of molecular remission in follicular lymphoma remains to be ascertained [117, 121], it is clear that idiotype vaccination either reduces the tumor burden beyond that already achieved by chemotherapy or leads to the redistribution of residual tumor cells to sites other than peripheral blood. These two trials provide strong evidence for an antitumor effect of lymphoma-specific vaccination. A multicenter, prospective, randomized trial is being conducted to further evaluate whether idiotype vaccination results in long-term clinical benefit.

Although chemotherapy followed by idiotype vaccination with or without GM-CSF seems to be an effective regimen to immunize against lymphoma, several investigators are trying to improve this approach. One process under evaluation is the use of DCs pulsed with idiotype protein [77]. Results of the first clinical trial in patients with relapse follicular lymphoma have been encouraging, with evidence of both cellular immune responses and clinical responses in approximately 30% of patients. This promising outcome has prompted the use of DCs in patients in first remission [78] and has further energized the field with novel techniques trying to circumvent the cumbersome and costly process of generating an individually tailored vaccine. In this sense, recombinant idiotype proteins are now attainable for preclinical testing [122, 123] and one already has been the subject of a phase I-II clinical trial [122]. One alternative to the use of idiotype vaccine is the use of DCs pulsed with whole lymphoma lysate. This strategy may offer the opportunity to target potential yet undefined lymphoma antigens (other than idiotype), therefore widening the T-cell repertoire against lymphoma.

Another approach to idiotype vaccination for non-Hodgkin's lymphoma is based on animal and human studies, which have shown that, in an allogeneic setting, immunity to certain antigens could be transferred from the marrow donor to the patient [124–127]. The strategy entails the immunization of the immunologically competent and normal allogeneic donor with the idiotype vaccine derived from the recipient's tumor before harvesting the stem cells to be used in the transplant. This strategy may generate highly specific antilymphoma T cells that are capable of transferring antitumor-specific

immunity from marrow donor to recipient. This approach already has been used in a patient with multiple myeloma and demonstrated that a de novo anti-idiotype response could be transferred to the recipient [128, 129].

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Over the past few years there have been tremendous advances in the field of cellular and molecular immunology, improving our understanding of the interactions between the tumor-bearing host and the immune system. As we begin to widen our knowledge significantly, we will be in a position to better comprehend the barriers to successful immunotherapy for cancer. The development of therapeutic cancer vaccines is entering a new era in which specific molecules expressed on cells of the immune system or TAA are being targeted, with the hope of mounting an efficacious antitumor response. One of the reasons the immune system does not eradicate cancer cells seems to be that tumor cells do not display their antigens in ways that are recognized easily by CTLs. A growing understanding of the process of epitope enhancement is allowing the development of modified TAA with improved immunogenicity and objective clinical outcomes.

Ilya Ilyich Metchnikoff first described mononuclear phagocytic cells at the end of the 19th century. Since then, an impressive body of literature has documented the involvement of these cells in the host immune defense. The recognition of the fundamental role of APCs in the initiation of the immune response against tumors has become progressively clear; however, signals delivered by APCs may result in either activation or suppression of T-cell immunity, including the induction of peripheral tolerance. Strategies aimed at generating APCs that can polarize the immune response toward a Th1 phenotype have been developed successfully in preclinical models and now are being translated into the clinical arena [130]. The use of modified tumor cells (autologous and/or allogeneic) by themselves or in the format of a hybrid with APCs has erupted in the field, and very dramatic responses have been reported.

Despite the significant advances that are occurring in the field, cancer vaccine strategies need to be optimized to obtain more favorable clinical outcomes [131]. It is important that the type of patient is taken into account with this approach. Typically, phase I and some phase II clinical trials are performed on patients with advanced disease that have been exposed to several chemotherapy regimens. These patients may have a compromised antitumor response, and it is not known how much immunity is required to eradicate cancer from patients with advanced disease and a significant tumor burden. Perhaps cancer vaccines need to be tested in the setting of minimal residual disease or in patients with no evidence of disease after primary treatment. In these settings, clinicians will evaluate time to disease progression or relapse prevention, respectively. Careful consideration must be given to disease stabilization as a potential end-point of therapeutic cancer vaccines in patients with advanced disease.

In summary, it is critical that strategies being developed for cancer vaccines be based on clearly defined cellular and molecular targets. We must design rational combinations that act upon several cellular

types, including initiators of the immune response (APCs) and effector cells (T cells). Finally, thoughtful clinical trial design is imperative to evaluate cancer vaccines at this early stage. Given the abundance of concepts coming from the laboratories, the next decade presages unprecedented growth in the development of effective cancer vaccines.

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The author thanks *Dr. Dan L. Longo* for his critical comments, and *Ms. Kathleen Marshall* for the illustrations.

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Received April 25, 2002; Accepted for publication June 21, 2002.

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